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# Inhaled Corticosteroids and the Risk of Fractures in Older Adults

## A Systematic Review and Meta-Analysis

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## Abstract

**Background:** Inhaled corticosteroids (ICS) are commonly prescribed medications for the management of asthma and chronic obstructive pulmonary disease. It is well established that long-term use of these drugs may lower bone mineral density. However, whether ICS increase the risk of fractures remains unknown. Recent studies that have attempted to explore this risk have had conflicting results. We sought to explore the risk of ICS and fractures among older adults by conducting a systematic review and meta-analysis of the literature.

**Methods:** We systematically searched several databases, including MEDLINE, EMBASE and the Cochrane Library, to identify pertinent studies. Those studies that potentially met our inclusion criteria were identified by two reviewers. Relative risks (RRs) were pooled using the random effects model. We also explored dose-response by stratifying the analysis on high and low doses of ICS. Heterogeneity was assessed using the Q statistic and publication bias was assessed using the funnel plot.

**Results:** Thirteen studies, including four randomized controlled trials, were included in the review. The pooled RRs for hip fractures and any fractures were 0.91 (95% CI 0.87, 0.96) and 1.02 (95% CI 0.96, 1.08), respectively. When we restricted the analysis to users of high-dose ICS, the pooled RRs for any fractures and hip fractures were 1.30 (95% CI 1.07, 1.58) and 1.32 (95% CI 0.90, 1.92), respectively. The funnel plot did not show evidence of publication bias.

**Conclusion:** We found no association between the use of ICS and fractures in older adults. A slight increase in risk was seen in those using high-dose ICS. The significance of this association should be investigated further.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality both in industrialized and developing countries.[1] Inhaled corticosteroids (ICS) are considered mainstay therapy in the treatment of asthma and are frequently prescribed in the management of COPD.[2] ICS have been shown to lower bone mineral density in young adults.[3] Several studies have explored the risk of fractures with ICS.[4-6] However, results have been inconsistent mostly as a result of a

small sample size and different methodologies used among the studies. Although some studies have found a positive association with ICS and fractures,[5] others have failed to find such an association.[6] In light of the recent evidence suggesting a potential beneficial effect of ICS in combination with β-agonists in COPD,[7] the potential risk of fractures associated with these drugs continues to be an important public health concern. Therefore, we sought to explore the risk of fractures with ICS in older adults by conducting a systematic review of the literature. Specifically, we sought to quantify the risk of fractures with ICS by looking at different types of fracture as well as exploring any potential dose-response relationship.

## Methods

We systematically searched MEDLINE (1966–August 2007), EMBASE (1980–August 2007) and the Cochrane Library (issue 2, 2007) by using the following search strategy: 'glucocorticoids' (MeSH heading) or 'steroids' (MeSH heading) or 'corticosteroids' (MeSH heading) or 'inhaled glucocorticoids' (subheading); and 'fractures' (keyword) or 'hip fractures' (keyword) or 'femoral fractures' (keyword); and 'case-control' (keyword) or 'case-referent' (keyword) or 'randomized controlled trial' (subject heading). In order to check whether every article on the topic was retrieved, we performed a second search that introduced the words 'inhaled glucocorticoids' and 'fractures' in an unstructured fashion. We used a similar strategy to search the LILACS database (Latin America and Caribbean Health Sciences Literature) and we searched meeting abstracts using the ISI Proceedings database from its inception in 1990 to 2007. We also examined the references of every article retrieved and those of recent reviews of inhaled corticosteroids and fractures. We considered including any relevant article, irrespective of the language of the publication. Unpublished studies were not considered. All searches were carried out independently by an epidemiologist and an internist (Drs Mahyar Etminan and Saeedreza Ganjizadeh Zavareh) and the results were combined. We used the MOOSE criteria[8] for observational studies and the QUOROM criteria[9] for randomized controlled trials (RCTs) for the reporting of studies.

We included studies that satisfied the following criteria: (i) explicitly described exposure to ICS in older adults (>40 years of age); (ii) explicitly defined the outcome, mainly fractures; (iii) provided relative risks (RRs) or odds ratios (ORs) or presented enough data to calculate them; and (iv) controlled for confounding using statistical adjustment or matching in the study design. We included clinical trials, case-control and cohort studies and excluded cross-sectional studies as the latter do not allow for the inference of the temporal effect of the exposure and the outcome. We separated studies that evaluated the risk of fractures with ICS in patients with COPD and those that looked at the risk of fractures with ICS in the general population. Finally, we assessed dose-response by pooling the RRs of the lowest and highest doses across the studies. All studies were reviewed by two of the authors (Drs Mahyar Etminan and Mohsen Sadatsafavi) and disagreements were resolved by consensus. When two or more studies were based on the same population, we chose the one with the most recent publication date.

RRs were pooled using the random effects model. ORs were considered an approximation of RRs. In case the authors had not reported information on the risk of any fracture, or where risks were reported for different age groups and not on the whole population, risks across specific fracture sites or age groups were combined using the fixed effects model to obtain the summary rates for any fractures. Heterogeneity was assessed using the Q statistic and its bootstrap version with 1000 replications. Publication bias was assessed using a funnel plot. All analyses were done using the HEpiMA software version 2.3.[20]

## Results

Sixty-two studies were identified, of which 15 met our inclusion criteria, including seven case-control studies,[5,6,12-16] four cohort studies[17-19,21] and four RCTs.[4,7,10,11] Among the three studies based on the UK General Practice Research Database,[5,16,21] we chose the study by de Vries et al.[16] because it presented the most recent data. Therefore, 13 studies were included in the final analysis [table I].[4,6,7,10-19]

**Table I.** Characteristics of the studies included in the review

| Study | Country | Population | Study design | Mean age (y) | RR (95% CI) for hip fractures | RR (95% CI) for any fractures | Co-variables |
|---|---|---|---|---|---|---|---|
| Johnell et al.[4] | European countries | Pts with mild COPD | RCT | 52 | NR | 1.67 (0.40, 3.11) | NA |
| Scanlon et al.[10] | USA/Canada | Pts with mild to moderate COPD | RCT | 56 | NR | 0.68 (0.33, 1.38) | NA |
| Pauwels et al.[11] | European countries | Pts with mild COPD | RCT | 56 | NR | 2.73 (0.72, 4.06) | NA |
| Calverley et al.[7] | Multinational | Pts with COPD | RCT | 65 | NR | 1.06 (0.77, 1.46) | NA |
| Lee and Weiss[6] | USA | Cohort of Veteran Affairs pts with COPD | Nested case-control | 63 | NR | 0.97 (0.84, 1.11) | Co-morbidity, OC, previous hospitalization |
| Suissa et al.[12] | Canada | Population-based cohort of pts prescribed respiratory medication | Nested case-control | 81 | 0.89 (0.84, 0.95)† | 0.96 (0.91, 1.01) | Age, sex, respiratory drugs, OC |
| Vestergaard et al.[13] | Denmark | Community-based cohort | Case-control | 43 | 0.86 (0.78, 0.95)† | 1.01 (0.98, 1.04)† | Corticosteroids, respiratory disease, autoimmune disease, previous fractures, respiratory medications |
| Johannes et al.[14] | USA | Population-based cohort of pts with COPD/ asthma/emphysema | Nested case-control | 53 | NA | 0.96 (0.85, 1.08) | Demographics, medical conditions, OC, respiratory disease |
| de Vries et al.[15] | Netherlands | Pharmacy dispensing database | Case-control | 76 | 1.08 (0.91, 1.27) | 1.08 (0.91, 1.27) | Respiratory medications, respiratory disease, co-morbidity |
| de Vries et al.[16] | UK | General Practice Research Database | Case-control | 62 | 1.04 (0.89, 1.21) | 1.04 (0.97, 1.11) | Smoking status, BMI, duration of enrolment in the database, OAD severity, exposure to bronchodilators |
| Baltzan et al.[17] | USA | Women >65 years without previous hip fractures | Cohort | 76 | 0.59 (0.12, 2.0) | 0.59 (0.12, 2.0) | None |
| Lau et al.[18] | Canada | Community cohort of women >65 years | Cohort | 75 | 0.92 (0.75, 1.12) | 0.92 (0.75, 1.12) | Age, co-morbidity, OC, bisphosphonates, |
| Hubbard et al.[19] | UK | Pts with COPD or asthma | Cohort | 81 | NA | 0.94 (0.52, 1.7) | Age, sex, corticosteroids, respiratory medications |

**BMI** = body mass index; **COPD** = chronic obstructive pulmonary disease; **NA** = not applicable; **NR** = not reported; **OAD** = obstructive airway disease; **OC** = oral corticosteroids; **pts** = patients; **RCT** = randomized controlled trial; **RR** = relative risk; **†** = pooled estimate of RR within study.

**Table II.** Relative risks (RRs) and 95% CIs for any fractures

| Study | Number of studies | RR (95% CI) for any fracture | P heterogeneity |
|---|---|---|---|
| All studies | 13 | 1.02 (0.96, 1.08) | 0.0004 |
| Sensitivity analysis[a] | 12 | 1.00 (0.98, 1.02) | 0.43 |
| Community setting | | | |
| all studies[13,15-18] | 5 | 1.01 (0.99, 1.04) | 0.57 |
| cohort studies[17,18] | 2 | 1.02 (0.99, 1.04) | 0.48 |
| case-control studies[13,15,16] | 3 | 1.08 (0.93, 1.26) | 0.55 |
| COPD setting | | | |
| all studies[4,9-12,14,16,19] | 8 | 1.05 (0.93, 1.20) | 0.0001 |
| sensitivity analysis[a][4,9,10,12,14,16,19] | 7 | 0.96 (0.92, 1.00) | 0.55 |
| Study stratified by dose | | | |
| low dose[6,12-16,19] | 7 | 0.98 (0.94, 1.03) | 0.10 |
| high dose[6,12-16,19] | 7 | 1.30 (1.07, 1.58) | 0.002 |
| sensitivity analysis[b][6,12-16] | 6 | 1.19 (1.05, 1.36) | 0.14 |
| RCTs | | | |
| all studies[4,7,10,11] | 4 | 1.38 (0.77, 2.48) | 0.0004 |
| sensitivity analysis[a][4,7,10] | 3 | 1.08 (0.72, 1.62) | 0.17 |
| Case-control studies[6,12-16] | 6 | 1.00 (0.97, 1.03) | 0.32 |
| Cohort studies[17-19] | 3 | 0.91 (0.76, 1.10) | 0.78 |

a Analysis excluding the study by Pauwels et al.[11]

b Analysis excluding the study by Hubbard et al.[19]

**COPD** = chronic obstructive pulmonary disease; **RCTs** = randomized controlled trials.

The RR for any fractures (all studies) was 1.02 (95% CI 0.96, 1.08) [table II]. When we stratified the results to the community setting versus the COPD setting, the RRs were 1.01 (95% CI 0.99, 1.04) and 1.05 (95% CI 0.93, 1.20), respectively. When we stratified our analysis by dose, we found a slight increase in the risk of fractures among high-dose ICS users (RR 1.30, 95% CI 1.07, 1.58).

The pooled RR for hip fractures was 0.91 (95% CI 0.87, 0.96) [table III]. When we restricted the analysis to studies in the community setting, the RR was 0.96 (95% CI 0.86, 1.07), whereas the RR for the analysis in the COPD setting was 0.89 (95% CI 0.84, 0.95). We found no significant increase in the risk of hip fractures among high-dose ICS users (RR 1.32, 95% CI 0.90, 1.92).

We found some heterogeneity for the analysis for the 'any fracture' category. The source of this heterogeneity was found to be the studies by Pauwels et al.,[11] Hubbard et al.[19] and de Vries et al.[15]

The results of the funnel plot did not show evidence of publication bias (figure 1).

## Discussion

Our study is the first systematic review of both observational studies and RCTs that has specifically quantified the risk of ICS and fractures. The results of our meta-analysis do not confirm a positive association between ICS use and risk of fractures. The results are similar when we stratified our analysis to RCTs or observational studies. However, we did find a slight increase in the risk of any fractures with high-dose ICS use. The clinical significance of this increase is unknown. The decrease in the risk of hip fracture in our analysis is most likely spurious and probably a result of patients with moderate/severe COPD being less physically active, which may put them at a lower risk of fractures.

We found significant heterogeneity among the studies we identified. This heterogeneity may have arisen as a result of the different methodologies and study design among the studies. More specifically, three studies were identified as the main source for this heterogeneity. As determined by our sensitivity analysis in which we excluded these studies (table II and table III), the sources of heterogeneity were the

**Table III.** Relative risks (RRs) and 95% CI for hip fractures

| Study | Number of studies | RR (95% CI) for hip fractures | P heterogeneity |
|---|---|---|---|
| All studies | 6 | 0.91 (0.87, 0.96) | 0.09 |
| Community setting | | | |
| all studies[13,15-18] | 5 | 0.96 (0.86, 1.07) | 0.84 |
| cohort studies[17,18] | 2 | 0.91 (0.75, 1.10) | 0.48 |
| case-control studies[13,15,16] | 3 | 0.98 (0.84, 1.14) | 0.023 |
| sensitivity analysis[a][13,16] | 2 | 1.06 (0.95, 1.18) | 0.74 |
| COPD setting | | | |
| all studies[12] | 1 | 0.89 (0.84, 0.95) | NA |
| Study stratified by dose | | | |
| low dose[8,9,11,12] | 4 | 0.90 (0.84, 0.96) | 0.55 |
| high dose[8,9,11,12] | 4 | 1.32 (0.90, 1.92) | 0.09 |

a Analysis excluding the study by de Vries et al.[15]

**COPD** = chronic obstructive pulmonary disease.

studies by Hubbard et al.[19] (for the dose-response analysis), Pauwels et al.[11] and de Vries et al.[15]

The study by Hubbard et al.[19] was a cohort study using data from the MRC (Medical Research Council) trial, a UK-based trial of the management of older people in the community.[22] Unlike the other studies, this study controlled for potential risk factors including alcohol intake, smoking and previous risk of fractures, which may have been the reason for a slight increase in the risk of fractures. Another reason for this heterogeneity may be the higher age and the difference in the patient population in this study as this was the only study that included both patients with COPD and patients with asthma.[19]

The study by Pauwels et al.[11] was an RCT of patients with mild COPD who were also smokers. Study patients were randomized to budesonide 400 μg and were followed for 3 years. The study population may have had a different risk profile compared with other studies that captured subjects with more severe COPD.[10] Similarly, budesonide is more potent than triamcinolone, a drug that was not used in other RCTs.[7]

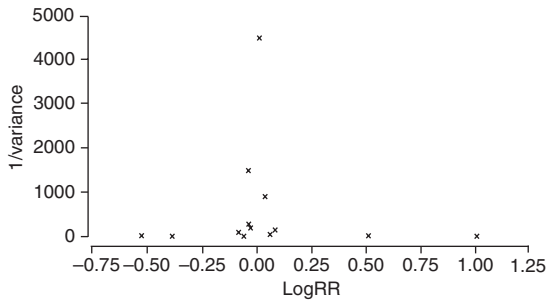


**Fig. 1.** Funnel plot for the studies of inhaled corticosteroids and any fracture. **RR** = relative risk.

The study by de Vries et al.[15] was a case-control study that assessed the effect of both oral and ICS with respect to fractures. In this study, the authors adjusted for respiratory disease severity, co-morbidity and prescription drugs (including antipyschotics and anticonvulsants), which may have resulted in a non-statistically significant increase in the risk of hip fractures.

Our review is subject to several limitations. First, most of the studies included in this review are observational studies − mostly case-control and cohort studies. Unlike RCTs, the major sources of bias in observational studies are recall bias as well as confounding bias. It is unlikely that recall bias will have affected the results of the individual studies as exposure status was captured mainly through computerized pharmacy records rather than patient interviews or questionnaires. Although an attempt was made to control for confounding in most of the observational studies, mainly in the study design or statistical analysis, it is still possible for confounding to have affected the results because many studies did not control for major risk factors or other confounders. For example, smoking may be a potential confounder which was not controlled for in most of the studies. It has been shown that patients who smoke are less likely to achieve a therapeutic response from ICS.[23] Therefore, it is possible that in studies where

this is not taken into account, the potential systemic effects of ICS may be underestimated. Finally, the slight increase in the risk of fractures among high-dose ICS users may be related to disease severity and not necessarily the effect of ICS.[24]

## Conclusion

The results of our systematic review are not consistent with an increase in the risk of fractures with the use of ICS in older adults. There was a slight increase in the risk of any fracture with the use of high-dose ICS, but this is probably not clinically significant. The association between ICS use and fractures should be evaluated further in future studies.

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